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Current treatments for renal cell carcinoma

Noble, H., & Walsh, I. (2015). Current treatments for renal cell carcinoma. *British Journal of Healthcare Management*, 21(6), 278-281. <https://doi.org/10.12968/bjhc.2015.21.6.278>

Published in:
British Journal of Healthcare Management

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

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Kidney Cancer – a current overview.

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Epidemiology and presentation

Renal cell carcinoma (RCC), also known as kidney cancer, renal adenocarcinoma or hypernephroma, and metastatic RCC (mRCC) continues to increase worldwide causing a substantial epidemiological burden (Escudier & Gore 2010). RCC is the 8th most common cancer in the UK with over 10,000 new cases diagnosed annually and is more common in men with a male/female ratio of 8/5 (Cancer Research UK 2104). It accounts for up to 90% of renal malignancies. mRCC is associated with a poor prognosis and up to 30% of people with RCC may present with metastatic disease at diagnosis. Up to 30% of patients who undergo surgical removal of a cancerous kidney (nephrectomy) may experience disease recurrence with the development of metastases (Poonacha et al 2011).

RCC is the third most common urological cancer (after prostate and bladder cancers) and is most commonly detected as an incidental finding on abdominal scanning performed for other reasons. If present, symptoms and signs may include blood in urine, a lump, pain, loss of appetite, weight loss or anaemia; none of which may be evident in the early stages of the disease. RCC is primarily found in people aged 50-70 years of age and may be caused by multiple factors, which include smoking, obesity, high blood pressure and a family history of the disease (Escudier & Gore 2010). Over 80% of kidney tumours are RCCs, occurring in the substance of the kidney (cortex). Some RCCs may develop in suspiciously appearing renal cysts, which may be undergoing clinical follow-up with sequential imaging (discussed below). Most of the remaining “kidney” cancers are transitional cell tumours arising in the renal pelvis and/or ureter (see figure 1).

Investigation and Staging

Several tests are deployed in the diagnosis and staging of RCC; these include physical examination, urine/blood tests and scanning. Imaging can range from plain x-rays of kidney,

ureter and bladder (KUB) and simple ultrasound scanning (US), through computerised tomography (CT) to magnetic resonance imaging (MRI) and intravenous pyelography (IVP). Metastatic disease can be evidenced by chest x-rays and adioisotope scans. Biopsies of suspected metastatic disease may be considered when planning management and are usually performed under imaging control by an interventional radiologist. Staging of RCC will largely direct clinical management. Staging is from stage I-IV on the basis of tumour size and extent of spread within, beyond and distant to the affected kidney:

Stage 1 - Early stage kidney cancer. Tumour measures up to 7cm, no bigger than a tennis ball and confined to the kidney.

Stage II – As for Stage 1, but tumour ≥ 7 cm.

Stage III -

- Tumour does not extend beyond kidney. Cancer cells spread through lymphatic system, or;
- Tumour invaded adrenal gland or tissue surrounding kidney, but cancer cells not spread beyond the fibrous tissue, or;
- Cancer cells spread from kidney to blood vessel.

Stage IV -

- Tumour extends beyond fibrous tissue surrounding the kidney, or;
- Cancer cells in more than one nearby lymph node, or;
- Cancer spread to other organs e.g lungs, bone.

Treatment

Clinical management is largely dictated by tumour stage. Treatment is considered and planned at multidisciplinary team (MDT) consultation involving Urologists, Radiologists, Pathologists and Oncologists. Factors to be taken into consideration include patient factors such as general health, co-morbidity, age and patient choice. Surgical intervention with radical nephrectomy is with the intent to effect cure (Nabi et al 2012). If RCC is present in both kidneys, the surgical approach becomes more complex; including techniques such as partial nephrectomy on one or both sides in an effort to preserve remaining healthy renal tissue and kidney function. Intervention with bilateral radical nephrectomy, will necessitate renal dialysis, whereby the blood is purified using a machine outside of the body. Such dialysis may be lifelong in the absence of a subsequent renal transplant. Transplantation may be contraindicated until at least two years have elapsed since complete tumour clearance. A waiting period may not be necessary if the original RCC was of early stage (Morath et al,

2004). Consideration of transplantation will be delayed for a longer period if the original kidney tumour was not of RCC type (Adami et al, 2003)

All of these radical surgical approaches can nowadays be performed via keyhole (laparoscopic) surgery. This minimally invasive approach is increasingly performed with the assistance of robotic technology, allowing the operating surgeon to perform and direct the surgery remotely. Additional minimally invasive techniques include radiofrequency ablation (removal of tissue using high frequency microwave currents), or cryotherapy (destruction of tumour with subzero temperature probes), which have led to dramatic improvement in treatment-related morbidity over the last decade (Farrell et al, 2003)

Arterial embolization may also be used to shrink a RCC prior to surgical intervention (Loffroy et al, 2010). This involves passing a catheter via a major blood vessel into the kidney. Materials such as gelatin sponges or metallic coils can then be introduced through the catheter, blocking blood flow and depriving the RCC of its' oxygen supply (Loffroy, 2015).

Additional therapy may be required or considered. This may be in an attempt to improve cure rates (adjuvant treatment) or to treat locally advanced or metastatic disease. Such intervention will be considered at the original MDT consultation and further discussed following surgery, when fully accurate tumour staging and grading is available. Whilst RCC is largely resistant to chemotherapy and radiotherapy, some encouraging, albeit limited, results can be achieved. Radiation therapy works by eradicating cancer cells and stopping or slowing their regrowth. External beam radiotherapy directs radiation from a machine outside the body toward the cancer under imaging, whilst internal therapy (brachytherapy) involves inserting radioactive material such as seeds or pellets via needles or catheters placed directly into or near the cancer.

Drug treatment

Chemotherapy acts to destroy cancer cells or attenuate their growth. This may prove somewhat effective for less common forms of kidney cancer, such as transitional cell tumours involving the renal pelvis or ureter (see figure 1). Whilst such drug treatment for RCC has been disappointing, encouraging results have been reported with drugs known as biological response modifiers (BRMs). These drugs include sunitinib, sorafenib, pazopanib, bevacizumab, interferon, interleukin everolimus and temsirolimus. Sunitinib is the most

commonly used BRM and is indicated for advanced disease. It acts by interfering with an enzyme (tyrosine kinase) within the cancer cells and thus interferes with their growth. The drug is taken in tablet form and whilst side effects are reported, results demonstrate significant tumour shrinkage and improved progression-free survival (Atkinson et al, 2014). Temsorilimus and everolimus are BRMs which work on a different enzyme (mTor) than sunitinib and are used as a second treatment for advanced kidney cancer in people who have had a previous biological therapy drug.

Interferon therapy boosts the patient's immune system (immunotherapy) to help fight the cancer and is usually given as a subcutaneous injection several times per week. Side effects include flu-like symptoms and fatigue; treatment has been used for advanced, recurrent or relapsed disease (Rini et al, 2010). Immunotherapy can also be provided with interleukin treatment, which has more severe side effects. Sorafenib acts by stopping signals which tell cancer cells to grow and prevents cancer cells forming blood vessels, which they need to grow, resulting in improved progression-free survival (Escudier et al, 2007, 2010)

Palliative Treatment

In the event of incurable disease, palliative treatment may also include chemotherapy or radiation therapy for localised metastatic disease, such as painful bony metastasis or spinal cord compression. Oral or intravenous steroid drug treatment may provide additional symptomatic relief.

Prognosis

Because most patients are diagnosed incidentally when the RCC is relatively localized and amenable to surgical removal, over 80% of patients with RCC survive for 5 years (National Cancer Institute, 2014). Patients with advanced disease fare less well; an average of less than 10% of patients survive longer than 5 years (American Cancer Society 2013)

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Figure 1 – diagram of the kidney

